The claims have been revised to define the invention with additional clarity. That the claims have been revised should not be construed as an indication that Applicants agree with any view expressed by the Examiner. Rather, the revisions are made merely to advance prosecution and Applicants reserve the right to pursue any deleted subject matter in a continuation application. The claims have not been revised to include sequence identifiers as the sequences set forth in the claims are only 9 nucleotides long.

Claims 1-6 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions and for the reasons that follow.

The term "functional equivalent thereof" is defined in the specification in the paragraph bridging pages 3 and 4 as "any nucleotide sequence capable of binding an Smad protein either individually or as part of a complex of Smad proteins whereby such binding is a necessary step for TGFβ and activin regulation of genes under the control of such functionally equivalent sequence". In view of this definition, the skilled person would have had no doubt as to what function Applicants refer with this language.

Reconsideration is requested.

Claims 1-6 stand rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. Withdrawal of the rejection is believed to be in order in view of the above-noted claim revisions and comments that follow.

Claims 1 and 6 have been amended to read "one or more Smad proteins selected from Smad2 spliced in exon 3, Smad3 and Smad4. Attention is directed to page 3 of the subject specification, second paragraph, for support (see also pages 25 and 26 regarding Smad3 and Smad4, and page 26, second paragraph, to page 28 regarding Smad2 spliced in exon 3).

Claims 1 and 6 have also been amended to include the listing of diseases/disorders recited in now cancelled claim 5.

The Examiner indicates that the specification provides insufficient guidance to permit practice of the claimed invention. That invention, a screening method, is in fact fully exemplified at pages 28-33. The skilled person would be well capable of carrying out such a screen, based on the description given, and of analyzing whether a given agent showed the desired activity in the screen. The present claims do not purport to directly cover a method of

treating diseases, merely to provide a tool for identifying agents that could be used in such treatment.

In view of the above, reconsideration is requested.

Claims 1-6 stand rejected under 35 USC 103 as allegedly being obvious over Yingling et al. The rejection is traversed.

In rejecting the claims as obvious, the Examiner cites Graham v John Deere. Using the test set forth therein, Applicants offer the following.

A) Determine the scope and content of the prior art

Yingling discloses, as is summarized in the abstract of the paper, that the Smad3/Smad4 complex has at least two separate nuclear functions:

1. it forms a rapid, yet transient, sequence-specific DNA binding complex, and

2. it potentiates AP-1 dependent transcriptional activation.

Yingling states that mutations which eliminate the Smad DNA binding site do **NOT** interfere with either TGF-β-dependent transcriptional activation or activation by Smad3/Smad4 co-overexpression. Therefore, the conclusion that the person skilled in the art would have reached is that the Smad DNA binding site is **NOT** essential for

transcriptional activation. Therefore, it would not have been obvious to use a Smad DNA binding sequence in an assay for screening for therapeutic agents for use in combating diseases associated with gene regulation by one or more Smad proteins and TGFβ or activin, since Yingling appears to demonstrate that that binding sequence is not essential for transcriptional activation.

B) Ascertain the differences between the prior art and claims

In direct contrast, Applicants have shown that their specifically identified CAGA box sequence confers TGF-β mediated induction (TGF-β-dependent transcriptional activation) and that a mutation of that sequence is unable to confer such induction (see Fig. 1(B) and (C)). Applicants detail a method of utilizing these findings in the form of a screening assay.

C) Resolve the level of ordinary skill in the art

The person of ordinary skill in the art would have read and understood the overall teaching of the available art and would have had a working knowledge of relevant laboratory techniques.

D) Consider objective evidence in the application indicating obviousness or non-obviousness

The Yingling paper teaches away from the findings of Applicants, so that the person skilled in the art would not have been motivated, on reading the paper, to seek an assay as claimed in claim 1 which utilizes the identified specific sequence. In light of the apparent contradiction between the findings of the Yingling and of the present invention, it is submitted that the present claims would not have been obvious over the citation.

Yingling also states, page 7020 first paragraph, that the Smad binding sequence is found in the natural PAI-1 promoter and he therefore speculates that the ability of Smad3/4 to directly bind DNA may have physiological relevance in regulating transcription of TGF-β responsive genes. In light of Yingling's own very clear findings to the contrary, this supposition is, at best, merely an invitation to experiment. This is not the appropriate test for obviousness.

Reconsideration is requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page/s is/are captioned "**Version With Markings To Show Changes Made**."

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This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

1. (Amended) A method for screening therapeutic agents for use in combating [diseases] fibrotic disorders, abnormal wound healing, abnormal bone formation, cancer development, haematopoiesis, neuroprotection and immune and inflammatory disorders where associated with gene regulation by one or more Smad proteins selected from the group consisting of Smad2 spliced in exon 3, Smad3 and Smad4 and TGFβ or activin, said method comprising detecting or assaying the extent or result of transcriptional activity or binding in the presence of said agent between a Smad protein or a DNA binding fragment thereof and a double strand oligonucleotide comprising the sequence 5' WXYCAGACZ 3' or a functional equivalent thereof, wherein in said nucleotide sequence W represents A or G, X represents G or T, Y represents C, A, G or T and Z represents A or C.

Cancel claim 5 without prejudice.

6. (Amended) A kit for screening agents [suitable] for combating [diseases] fibrotic disorders, abnormal wound healing, abnormal bone formation, cancer development,

haematopoiesis, neuroprotection and immune and inflammatory disorders where associated with gene regulation by one or more Smad proteins selected from the group consisting of Smad2 spliced in exon 3, Smad3 and Smad4 and TGFβ or activin, said kit comprising:.

- a Smad protein [as hereinbefore defined]
- TGFβ or activin
- a double strand DNA molecule comprising the sequence 5' WXYCAGACZ 3' or a functional equivalent thereof, wherein in said nucleotide sequence W represents A or G, X represents G or T, Y represents C, A or G and Z represents A or C[, said sequence optionally being in operable linkage with a promoter or enhancer sequence and coding region of a gene whose product is detectable].